# MDMA-AT, PTSD, & Comorbid OCD:
## A systematic review of the potential effects of 3,4-methylenedioxy-methamphetamine - assisted therapy for PTSD on comorbid OCD

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## INTRODUCTION

- **MDMA-Assisted Therapy (MDMA-AT):** Breakthrough psychedelic treatment for post-traumatic stress disorder (PTSD) [1]
- Currently completing phase 3 FDA clinical trials; FDA approval estimated by 2023
- But PTSD & OCD are **highly comorbid** psychiatric conditions within PTSD patient populations (40%) [2 3 4 5]
  - Far superseding the 1-3% prevalence rate of OCD in the general population [6]

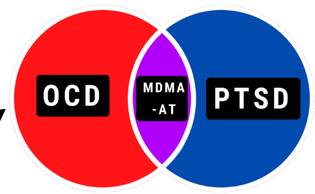
Approximately 40% of patients with PTSD are diagnosed with comorbid OCD

- PTSD & OCD treatments fundamentally differ in their execution, with PTSD psychotherapy being **contraindicated** for OCD [7 8 9 10 11]
- Patients with comorbid PTSD & OCD also experience **more severe OCD symptomology** than patients with *just* OCD [12 13 14 15]
- ***Therefore, PTSD patients with comorbid OCD are a highly vulnerable, at-risk population when studying and administering PTSD treatments***

## RESEARCH QUESTION

Thus, when studying the potential of MDMA-Assisted Therapy for PTSD, a notable point of consideration is:

**What are the potential effects of MDMA-Assisted Therapy for PTSD on comorbid OCD?**




## REVIEW OBJECTIVES

- Overview **relevant features** of OCD, PTSD, and their comorbid nature
- Evaluate potential effects of MDMA-AT for PTSD on comorbid OCD across **various levels**:
  - Psychotherapy conduction & clinical design
  - Pharmacological mechanisms
  - Neuropsychopharmacological properties
- Discuss conclusions, recommendations, and future directions of current research question

## OVERVIEW OF OCD

**OCD: Obsessive-Compulsive Disorder**

- **Obsessions:** Recurrent and persistent thoughts, urges or images that are experienced as intrusive, and unwanted, and that in most individuals cause marked anxiety or distress. [16]
  - The thoughts, impulses, or images are not simply excessive worries about real-life problems.
- **Compulsions:** Repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly. [16]
  - *Mental Compulsions:* **can be very similar to or overlap with PTSD symptoms**
    - **Examples:** rumination, mental review, thought neutralization, compulsive prayer, reassurance-seeking, avoidance, etc.

## OVERVIEW OF PTSD

**PTSD: Post-Traumatic Stress Disorder**

- Psychiatric disorder that may occur in people who have experienced or witnessed a traumatic event, and then are plagued with disturbing thoughts and feelings related to their experience that last long after the traumatic event has ended. [16]
- **4 Symptom Clusters:** [16]
  - Intrusive memories or thoughts
    - Also referred to as "re-experiencing"
  - Avoidance
  - Alterations in cognition and mood
  - Alterations in arousal and reaction
- Symptoms of PTSD are very similar to certain OCD symptoms and behaviors

## OVERVIEW OF COMORBIDITY

- **High Comorbidity:** 40% of PTSD patients have comorbid OCD, which greatly supersedes the 1-3% prevalence rate of OCD in the general population [2 3 4 5 6]
- **Contraindication:** PTSD psychotherapy is unhelpful and actively harmful to OCD [17]
  - Contraindicated psychotherapies include: traditional cognitive-behavioral therapy (CBT), exposure therapy, psychodynamic therapy, and eye-motion desensitization & reprocessing therapy (EMDR)
  - Correct OCD psychotherapy: exposure & response prevention therapy (ERP) [18 19]
- **Functionally Dynamic Relationship:** OCD & PTSD symptoms can be dynamically related [20 21 22 23 24]
  - Obsessions can be rooted in traumatic experiences/beliefs
  - Compulsions can be used to cope with traumatic stress (e.g. thought neutralization, avoidance, etc.)
- **More Severe Symptomology:** Patients with comorbid PTSD and OCD experience more severe OCD symptomology than patients with *just* OCD [25 26 27]

## REVIEW OF MDMA-AT PSYCHOTHERAPY

**MDMA-Assisted Therapy Protocol is sourced from the current paradigm for MDMA-Assisted Therapy for PTSD: FDA Phase 3 Clinical Trial Procedures** [1]

**Screening Tests:**

- No Y-BOCS test to screen out OCD
- Tests used in clinical trial do not screen out for OCD

**Exclusion Criteria:**

- Does not explicitly include those with OCD or obsessive-compulsive related disorders from participation

**Psychotherapy Conduction:**

PTSD therapies contraindicated for OCD: [28 29 30 31 32]

- Traditional cognitive-behavioral therapy (CBT)
- Exposure therapy
- Psychodynamic therapy

## REVIEW OF MDMA-AT PHARMACOLOGICAL MECHANISMS

**Potential OCD & MDMA Interactions:**

MDMA may *potentially* pharmacologically benefit and harm *certain aspects of* known OCD pathophysiology

| OCD Pathophysiology | Current Treatments | MDMA Mechanisms |
|---|---|---|
| Cortico-striatal hyperactivity = excessive grooming behavior [33] | Serotonin reuptake inhibitors (SRIs) [40] | 5HT1A, 5HT2A-C, & D1-2 Agonist [47 48] |
| Serotonin transporter overactivity [34] | Norepinephrine reuptake inhibitors (NRIs) [41] | Blocks SERT, NET, & DAT [49] |
| SAPAP3-mediated MGlur5 overactivity [35] | Deep brain stimulation (DBS) in various cortico-striatal-thalamic targets [42] | SERT, NET, & DAT reverse transport [50] |
| D2/3 oversignaling in ventral striatum [36] | D2 receptor antagonists [43] | D2 receptor agonist [51 52] |
| Glutamatergic oversignaling in the direct Dopamine receptor type 1 striatal pathway [37] | Glutamatergic modulators [44] | Increases glutamatergic signaling [53] |
| Thalamo-amygdala circuit hyperactivity [38] | Transcranial magnetic stimulation (TMS) in various cortico-striatal-thalamic targets [45] | Reduces amygdalar activity & enhances fear extinction learning [54 55] |
| Amygdalar hyperactivity [39] | Deep brain stimulation (DBS) in nucleus accumbens [46] | Oxytocin-dependent LTD in nucleus accumbens [56] |

**Potential medication benefits of MDMA for OCD:**

- MDMA can be administered less frequently (yearly, semi-yearly) versus daily SSRI/SNRI medication administration
- Lowered costs of administration due to lowered frequency
- Far less invasive treatment than DBS
- Can potentially aid in correction of excessive mGlur5 signaling in OCD due to neuropharmacological properties

## REVIEW OF MDMA-AT NEUROPSYCHOPHARMACOLOGY

**MDMA Reopens Social Critical Learning Period**

- **Critical Learning Period:** A hyperplastic state for change that generally open throughout earlier periods of life & then closes.
  - *Examples: Language learning, social influence during adolescence, sensitive periods of recovery after stroke, early intervention periods for blindness and deafness, etc.*
- A long-time neuroscience goal has been to **reopen** these CLPs to potentially harness them for therapeutic use…
- And MDMA has been shown to reopen them! [56]
  - CLP is reopened by MDMA for 2-3 weeks in mice
  - Which can (very roughly) translate to anywhere from **2 months to 1 year in humans**
- Proposed **mechanism of action** for MDMA reopening CLP: oxytocin-dependent long-term depression (LTD) in the nucleus accumbens [56]
  - MDMA readily crosses the blood-brain barrier, solving the therapeutic issue of oxytocin administration previously not crossing

**Potential implications of reopening CLPs on MDMA-AT:**

- The role of MDMA in MDMA-assisted therapy far exceeds just the "trip"
- "Psychotherapy"/integration aspect of MDMA-assisted therapy is crucial
- Therapist & therapies conducted are of utmost importance
- *The implications when the incorrect/contraindicated treatments are conducted?*

## CONCLUSIONS

- Current screening, exclusion, & psychotherapy conduction practices of MDMA-AT do not consider comorbid OCD & can ultimately be harmful to those with comorbid OCD
- MDMA may be pharmacologically beneficial and harmful to varying parts of OCD pathophysiology, and may have administration benefits
- However, when MDMA is coupled with psychotherapy practices of MDMA-AT, reopening of critical learning periods may **greatly amplify** harmful effects of contraindicated PTSD psychotherapies

## PRIMARY RECOMMENDATIONS

- ✓ **OCD Screening:** Include a Y-BOCS test in assessments for MDMA-AT for PTSD eligibility due to high comorbidity rate
- ✓ **OCD Exclusion:** Explicitly list OCD and the entire class of obsessive-compulsive related behavior disorders as exclusion criteria for MDMA-AT for PTSD
- ✓ **ERP Training:** Explore training MDMA-AT clinicians to recognize repetitive & compulsive behaviors (especially mental compulsions & behaviors that may resemble PTSD symptoms) and administer basic response prevention

## FUTURE DIRECTIONS

- ❑ Studying MDMA & MDMA-assisted therapy in OCD
- ❑ Studying psychedelic-assisted therapies for OCD
- ❑ Developing further psychotherapeutic frameworks for treating comorbid OCD & PTSD with higher efficacy
- ❑ Studying the mechanistic underpinnings of MDMA & other psychedelics (psilocybin, DMT, etc.) in pre-clinical models
- ❑ Elucidating further neurobiological/pathophysiological circuits and functions of OCD
- ❑ Studying the overlap and differentiation of OCD & PTSD neurobiological/pathophysiological circuits

## REFERENCES

Scan this QR code to. view list of references:

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